

APPLICANT: Carpenter
SERIAL NO.: 09/178,035

At the Examiner's suggestion, Applicant has amended claim 8 to recite --further comprising heparin-- to more clearly define this limitation.

THE § 112, FIRST PARAGRAPH, REJECTION

The Examiner has rejected claims 7-8 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification, while being enabling for a particular defined culture medium formulated to promote neural stem cell proliferation, does not provide enablement for using the components encompassed by the conventional culture medium ingredients. Applicants traverse.

One of skill in the art could, using the disclosure of the patent application, successfully and without undue experimentation formulate a culture medium which allows neural stem cell proliferation (and not their differentiation), as well as to determine the appropriate amount of each component so as to successfully cause such an effect. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 1606 (1987); MPEP § 2164.01. The specification provides preferred ranges for components of a culture medium containing LIF which is effective for proliferating neural stem cells (*see*, specification, pg. 5, lines 1-8). The specification also provides guidance for assaying media effective for neural stem cell proliferation. For example, the cell culture can be tested for the presence of neurospheres (*see*, specification pg. 12, lines 3-5, 18-20; FIG. 1) or for the presence of nestin-positive cells or the relative absence of GFAP-positive and β -tubulin cells (*see*, specification, pg. 6, lines 7-10; pg. 12, lines 21-26; FIG. 2; FIG. 3). The specification provides a working example of a defined culture medium comprising numerous essential ingredients including leukemia inhibitory factor (LIF) within the recited concentration ranges that in fact promotes and enhances viable neural stem cell-proliferation therein (*see*, specification, pg. 11, EXAMPLE 1) compared to prior art media lacking LIF (*see*, specification, pg. 3, lines 21-26; *see*, *e.g.*, WO 93/01275, WO 94/16718).

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Nevertheless, to advance prosecution and in response to the Examiner's suggestion, Applicant has amended the claims to recite concentration ranges for the limitation in claim 7(b)-(e). Accordingly, Applicant requests that this rejection be withdrawn.

THE § 112, SECOND PARAGRAPH, REJECTION

The Examiner has rejected claims 7-8 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner has made several suggestions as to how the claims could be amended to overcome these rejections. Applicant has amended the claims accordingly.

This rejection is now moot and should be withdrawn.

THE § 103 REJECTION

The Examiner has rejected claims 7-8 under 35 U.S.C. § 103(a) as allegedly unpatentable over Johe, United States patent 5,753,506 ("*Johe*") in view of Gay, United States patent 5,639,618 ("*Gay*"). Applicants traverse.

The Examiner has not set forth a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, (1) there must be some suggestion or motivation to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art references must teach or suggest all the claim limitations. MPEP § 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. Here, there is no motivation to combine *Johe* and *Gay*, no reasonable expectation of achieving a successful culture medium for proliferating viable human neural stem cells by combining *Johe* and *Gay*, and no combined culture medium which teaches all the limitations of the claimed invention.

The invention provides a culture medium for proliferating viable human neural stem cells (see, specification, pg. 3, line 15). The claimed culture medium is thus distinguished from the *Gay* LIF-containing medium, which does not refer to proliferating neural stem cells -- rather, *Gay*

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describes cultures of embryonic stem cells (*see, Gay*, col. 5, 62-65; col. 7, lines 5-12). *Gay* discloses a standard medium for the maintenance of embryonic stem cells. Among the factors required for embryonic stem cell maintenance are 15% fetal calf serum, LIF, bFGF, and Steel factor (SF). All these factors are required; the requirement for LIF is not separate from the other factors. The *Gay* medium contains serum, which would not permit neural stem cell proliferation. Any amount of LIF disclosed by *Gay* is thus irrelevant to neural stem cells. Further, the *Gay* LIF-containing medium (*see, Gay*, col. 7, lines 5-12) is not a culture medium for differentiating embryonic stem cells to neural stem cells (*compare to, e.g., Gay*, col. 8, lines 18-21), as alleged by the Examiner. ✓

The claimed medium is also distinguished from media for differentiating neural stem cells to form differentiated neural cells (*i.e., the Johe* medium). The *Johe* culture medium for differentiating neural stem cells does not contain the claimed growth factors (*e.g., EGF, TGF, bFGF, aFGF*) or heparin (which is used in conjunction with aFGF) (*see, Johe*, col. 7, lines 61-65, “medium without the growth factor”). The *Johe* differentiation media may include LIF (*see, Johe*, col. 8, line 1-5), but as a differentiating agent in the presence of conditions that preclude neural stem cell proliferation. ✓ ←

One skilled in the cell culture art would not have expected that a culture medium for differentiating neural stem cells would have been useful for proliferating neural stem cells. To the contrary, the skilled artisan would expect that a culture medium for differentiating neural stem cells that contains LIF is not useful for proliferating neural stem cells.

Obviousness requires a reasonable expectation of success. *Ex parte Blanc*, 13 USPQ2d 1383 (BPAI 1989); MPEP § 2143.02. Here, one of ordinary skill in the cell culture art reading *Gay* or *Johe* (or both) would have expected LIF to be a differentiation factor for neural stem cells, not as a proliferation enhancer, as in the instant culture medium. The Examiner makes this very point in the Office Action.

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Further, it is well known in the art that LIF typically acts as a stem cell differentiating (morphogenic) agent (see, e.g., USP 5,753,506 - Johe, abstract and 7, line 66 - col 8, line 4) when added to a defined culture medium, and not as a stem cell-proliferating (mitogenic) agent as instantly claimed/disclosed.

(Office Action of April 28, 1999, Paper 4, pg. 3, lines 1-3). Likewise, the Examiner notes that

the preferred, demonstrated amount (10 ng/mL) of LIF within the instantly disclosed defined culture medium which causes neural stem cell proliferation (see, e.g., page 11, Example 1) is the same amount shown to cause differentiation when certain essential ingredients are removed (e.g., growth factor mitogens) and other essential ingredients are added (e.g., serum, mixture of other growth factors) - as shown in Example 4 (page 14), wherein LIF is removed from the stem cell-proliferating medium, . . .

(Office Action of April 28, 1999, Paper 4, pg. 3 lines 3-9).

The specification confirms this; "unexpectedly we have found that LIF dramatically increases the rate of cellular proliferation in almost all cases." (see, specification, pg. 3, lines 31-32).

Even if the combination of *Johe* and *Gay* were proper (which it is not), the combination would not lead to the claimed invention. In both *Johe* and *Gay*, when LIF is used, the factor is in the presence of serum or other culture conditions that preclude neural stem cell proliferation. To combine the factors in the *Gay* medium for the maintenance of embryonic stem cells (especially the 15% fetal calf serum) to the *Johe* culture media would simply not result in a neural stem cell proliferation medium. ✓

Applicant requests that this rejection be withdrawn.

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CONCLUSION

The pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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